# The ADO index as a predictor of two-year mortality in general practice-based chronic obstructive pulmonary disease cohorts

Abu Hussein, Nebal ; Ter Riet, Gerben ; Schoenenberger, Lucia ; Bridevaux, Pierre-Olivier ; Chhajed, Prashant N ; Fitting, Jean-William ; Geiser, Thomas ; Jochmann, Anja ; Joos Zellweger, Ladina ; Kohler, Malcolm ; Maier, Sabrina ; Miedinger, David ; Schafroth Török, Salome ; Scherr, Andreas ; Siebeling, Lara ; Thurnheer, Robert ; Tamm, Michael ; Puhan, Milo A ; Leuppi, Joerg Daniel

Abstract: BACKGROUND: Existing prediction models for mortality in chronic obstructive pulmonary disease (COPD) patients have not yet been validated in primary care, which is where the majority of patients receive care. OBJECTIVES: Our aim was to validate the ADO (age, dyspnoea, airflow obstruction) index as a predictor of 2-year mortality in 2 general practice-based COPD cohorts. METHODS: Six hundred and forty-six patients with COPD with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages I-IV were enrolled by their general practitioners and followed for 2 years. The ADO regression equation was used to predict a 2-year risk of all-cause mortality in each patient and this risk was compared with the observed 2-year mortality. Discrimination and calibration were assessed as well as the strength of association between the 15-point ADO score and the observed 2-year all-cause mortality. RESULTS: Fifty-two (8.1%) patients died during the 2-year follow-up period. Discrimination with the ADO index was excellent with an area under the curve of 0.78 [95% confidence interval (CI) 0.71-0.84]. Overall, the predicted and observed risks matched well and visual inspection revealed no important differences between them across 10 risk classes ($p = 0.68$). The odds ratio for death per point increase according to the ADO index was 1.50 (95% CI 1.31-1.71). CONCLUSIONS: The ADO index showed excellent prediction properties in an out-of-population validation carried out in COPD patients from primary care settings.

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# The ADO Index as a Predictor of Two-Year Mortality in General Practice-Based Chronic Obstructive Pulmonary Disease Cohorts

Nebal Abu Hussein[a, b] Gerben ter Riet[k] Lucia Schoenenberger[c] Pierre-Olivier Bridevaux[e] Prashant N. Chhajed[a, b] Jean-William Fitting[f] Thomas Geiser[g] Anja Jochmann[c] Ladina Joos Zellweger[d] Malcolm Kohler[h] Sabrina Maier[a, b] David Miedinger[a, b] Salome Schafroth Török[c] Andreas Scherr[c] Lara Siebeling[k] Robert Thurnheer[j] Michael Tamm[c] Milo A. Puhan[i] Joerg Daniel Leuppi[a, b]

[a]University Clinic of Internal Medicine, Kantonsspital Baselland, [b]University of Basel, [c]University Hospital Basel and [d]St. Claraspital, Basel, [e]Hôpitaux Universitaires de Genève, Geneva, [f]Centre Hospitalier Universitaire Vaudois, Lausanne, [g]Inselspital, Bern, [h]University Hospital Zurich and [i]Institute for Social and Preventive Medicine, University of Zurich, Zurich, and [j]Kantonsspital Muensterlingen, Muensterlingen, Switzerland; [k]Academic Medical Centre, Department of Primary Care, University of Amsterdam, Amsterdam, The Netherlands

**Key Words**
Chronic obstructive pulmonary disease · ADO index · Mortality prediction · Primary care

**Abstract**
***Background:*** Existing prediction models for mortality in chronic obstructive pulmonary disease (COPD) patients have not yet been validated in primary care, which is where the majority of patients receive care. ***Objectives:*** Our aim was to validate the ADO (age, dyspnoea, airflow obstruction) index as a predictor of 2-year mortality in 2 general practice-based COPD cohorts. ***Methods:*** Six hundred and forty-six patients with COPD with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages I–IV were enrolled by their general practitioners and followed for 2 years. The ADO regression equation was used to predict a 2-year risk of all-cause mortality in each patient and this risk was compared with the observed 2-year mortality. Discrimination and calibration were assessed as well as the strength of association between the 15-point ADO score and the observed 2-year all-cause mortality. ***Results:*** Fifty-two (8.1%) patients died during the 2-year follow-up period. Discrimination with the ADO index was excellent with an area under the curve of 0.78 [95% confidence interval (CI) 0.71–0.84]. Overall, the predicted and observed risks matched well and visual inspection revealed no important differences between them across 10 risk classes (p = 0.68). The odds ratio for death per point increase according to the ADO index was 1.50 (95% CI 1.31–1.71). ***Conclusions:*** The ADO index showed excellent prediction properties in an out-of-population validation carried out in COPD patients from primary care settings.



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E-Mail karger@karger.com
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Prof. Dr. med. et phil. Milo Puhan
Institute for Social and Preventive Medicine, Room HRS G29
University of Zurich, Hirschengraben 84
CH–8001 Zurich (Switzerland)
E-Mail milo.puhan@ifspm.uzh.ch

## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality worldwide and is therefore a major public health concern. With its prevalence rising, the WHO estimation is that it will be the third leading cause of death by 2030 [1, 2]. Many multidimensional indices like BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity), DOSE (dyspnoea, obstruction, smoking and exacerbation) and ADO (age, dyspnoea and airflow obstruction) have been developed to predict mortality in COPD [3–5].

In 2009, Puhan et al. [5] recalibrated and updated the BODE index in 2 separate European COPD cohorts. They recognised that the reduced distance in the 6-minute-walk-test had an even greater impact on mortality than in the original cohort in the USA. They also observed that age, dyspnoea and $FEV_1$ had a strong association with 3-year mortality and that these parameters could be used as predictors for mortality [5]. The new index was called the ADO index. It has the clear advantage that 6-minute-walk-test data are not required; it is often not practicable to perform this test in a general practice setting, so the ADO is more convenient than the BODE index. In a recent, large-scale validation in almost 14,000 patients with COPD from diverse settings, the ADO showed good predictive performance after updating the underlying regression equation (intercept and coefficients) [6]. However, ADO has not been investigated in purely general practice-based cohorts. Neither has its ability to predict mortality in a shorter time been assessed. Our aim was to assess the performance of the ADO index in predicting 2-year mortality in 2 general practice-based COPD cohorts, in Switzerland and the Netherlands.

## Material and Methods

*Study Design and Patients*

Data from 2 general practice-based COPD cohorts, namely the Swiss COPD Cohort and the International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts (ICE COLD ERIC) were pooled [7–10].

Swiss COPD Cohort Study

General practitioners (GPs) from all over Switzerland were invited to participate in the study; 139 agreed to participate and each recruited 1–20 patients (≥40 years of age) with presumed mild to very severe COPD according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The exclusion criteria were dementia or psychiatric morbidity and an inability to complete the questionnaires due to language difficulties [11, 12]. Each patient underwent a baseline assessment (demographic data, physical examination, spirometric parameters, medical treatment and exacerbation history) and was then followed for 24 months. Data were entered into a central online database either by the physicians or by the study team after receiving the collected data questionnaires by facsimile. The ethics committees of each canton with participating GPs approved the study protocol and all patients provided their written informed consent. For more details on this cohort, we referred to earlier publications [7, 8]. We used data from 2007 to 2010 for this study.

ICE COLD ERIC Study

In this ongoing, prospective, multi-centre cohort study, COPD patients from primary care were enrolled in the Netherlands and in Switzerland between April 2008 and August 2009 [9, 10]. At inclusion, all patients (≥40 years of age) had GOLD stage II–IV COPD and had been free of exacerbations for ≥4 weeks. The only exclusion criteria were a life expectancy of <12 months and dementia or psychotic morbidity. All patients provided their written informed consent. After a comprehensive baseline assessment, they were followed up every 6 months for up to 5 years. All data, in duplicate, were entered centrally into a database managed by the Clinical Research Unit of the Academic Medical Center Amsterdam, The Netherlands. The study was approved by all local ethics committees and is registered on ClinicalTrials.gov (NCT00706602). Detailed information about the study protocol and results are available elsewhere [9, 10]. None of the patients from the Swiss COPD cohort were included in the Swiss arm of this cohort.

*Measurement of Predictors and Mortality*

In both studies, age was recorded at baseline and all patients completed the modified Medical Research Council (mMRC) dyspnoea scale [13, 14]. Spirometry was performed according to the 2005 guidelines of the American Thoracic Society [15]. A spirometer (EasyOne™, ndd Medizintechnik AG, Zürich, Switzerland) was used in both studies to assess lung function as described previously [7, 8, 10]. All participating physicians were instructed on the usage of the spirometer and how to complete spirometry according to the guidelines. The lung function reference values compiled by Braendli et al. [16] were used in the Swiss management cohort. The ERS-ECCS reference equation as programmed into the EasyOne device was used as reference value in the ICE COLD ERIC. In both studies, all-cause mortality within 2 years was ascertained during follow-up assessments and confirmed by the GPs.

*Statistical Analysis*

We followed a standard approach for an external out-of-population validation of a prediction model. We first calculated the 2-year risk of all-cause mortality for each patient using the regression equation published recently [6]. We then assessed discrimination by calculating the area under the curve (AUC). For calibration, we adjusted the intercept for the primary populations studied here because we looked at 2-year mortality where the mortality rate is expected to be lower than the 3-year mortality rate predicted by the ADO model. We then assessed calibration by comparing the predicted and observed 2-year all-cause mortality across all patients (calibration at large) and for deciles of the

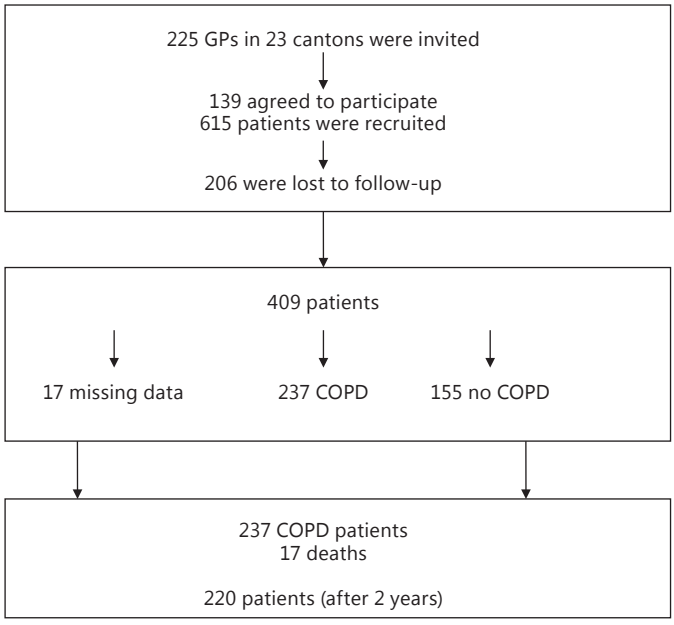


**Fig. 1.** Flow chart of the Swiss management COPD cohort.

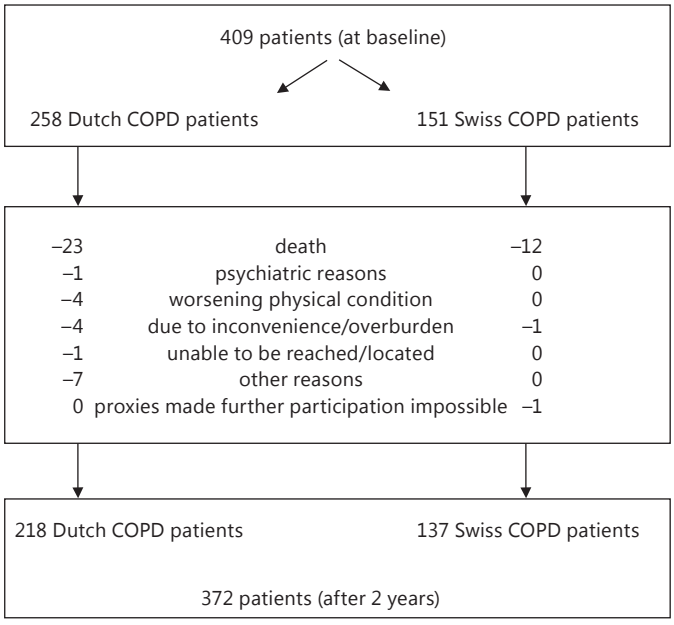


**Fig. 2.** Flow chart of the ICE COLD ERIC.

**Table 1.** Patients' baseline characteristics

| | Swiss COPD cohort (n = 237) | ICE COLD ERIC (n = 409) | | Pooled cohort (n = 646) |
|---|---|---|---|---|
| | | Dutch arm (n = 258) | Swiss arm (n = 151) | |
| Age, years | 67.6±10.8 | 66.4±10.3 | 67.4±9.3 | 67.4±10.3 |
| Male | 165 (69.6) | 130 (50) | 103 (68.2) | 398 (61.6) |
| Current smokers | 100 (42.7) | 104 (40) | 53 (35.1) | 257 (39.8) |
| BMI | 25.8±4.9 | 26.2±5.4 | 26.2±4.7 | 26±5.1 |
| $FEV_1$, % | 51.4±19.1 | 55.4±15.8 | 55.7±18.0 | 52.4±26 |
| MMRC dyspnoea scale | 1.4±1.3 | 2.3±1.6 | 1.1±0.9 | 1.7±1.4 |
| Diabetes mellitus | 21 (10.5) | 43 (16.5) | 20 (13.3) | 99 (15.3) |
| Coronary heart disease or heart failure | 43 (21.4) | 53 (20.5) | 25 (16.5) | 121 (18.7) |
| Cerebrovascular accident | 6 (3) | 23 (9) | 13 (9) | 42 (6.5) |

Values are mean ± SD or n (%).

risk distribution (i.e. 10 groups). We inspected the calibration plots visually and used the Hosmer-Lemeshow statistic to formally compare predicted and observed risks. We calculated the ADO score as recently published (from 0 to 14) for each patient. We used a logistic regression model with 2-year all-cause mortality as the dependent variable and the ADO score as the independent variable to compare the association [expressed as an odds ratio (OR)] and the AUC of the receiver-operating characteristic (ROC) with those observed in the large-scale ADO validation (OR 1.48 and AUC 0.82) [6]. We performed all analyses using STATA for Windows (v11.2).

## Results

The Swiss COPD cohort consisted of 237 patients (fig. 1) and there were 409 in the ICE COLD ERIC (Dutch arm: 258 and Swiss arm: 151; fig. 2). In total, 646 subjects were included in our analysis. The baseline characteristics are shown in table 1. On average, patients were 67.4 years old. In the Swiss cohort and the Swiss arm of the ICE cohort, approximately 70% were men.

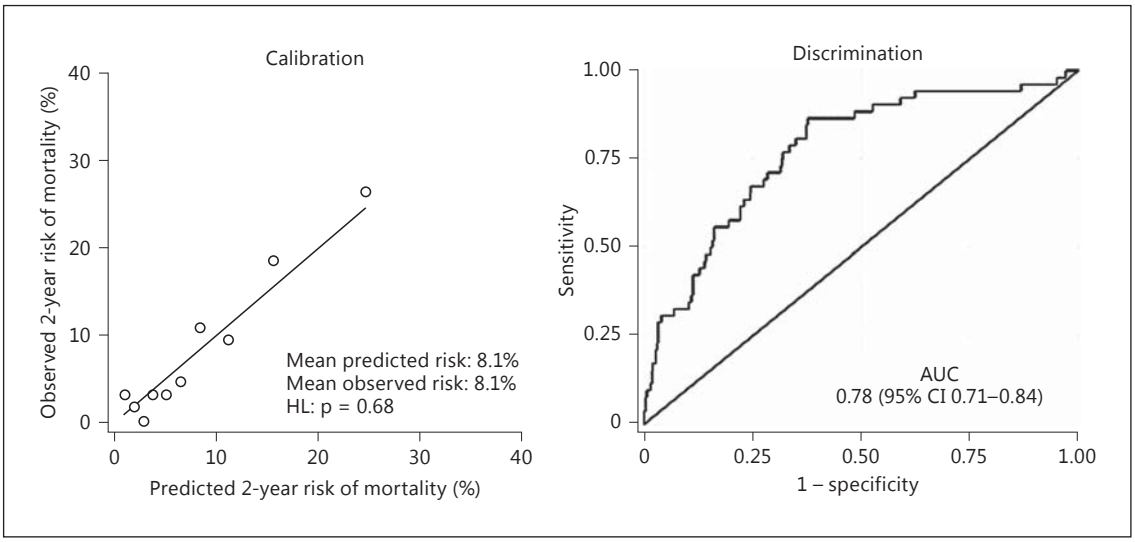


**Fig. 3.** Validation of the ADO index in COPD patients treated in primary care setting. The calibration curve shows the predicted and the observed risks of mortality. The discrimination curve illustrates the AUC.

**Table 2.** Lung function

| | Swiss COPD cohort (n = 237) | ICE COLD ERIC (n = 409) | | Pooled cohort (n = 646) |
|---|---|---|---|---|
| | | Dutch arm (n = 258) | Swiss arm (n = 151) | |
| GOLD I | 7 (2.9) | 0 | 0 | 7 (1.1) |
| GOLD II | 101 (42.6) | 173 (67.1) | 95 (62.9) | 369 (57.1) |
| GOLD III | 103 (43.4) | 63 (24.4) | 40 (26.5) | 206 (31.9) |
| GOLD IV | 26 (11) | 22 (8.5) | 16 (10.6) | 64 (9.9) |

Values are n (%).

Men made up 50% of the Dutch arm of the ICE cohort. The cohorts were similar in terms of patients' age, BMI and the frequency of comorbidities. The BMI average in the Swiss cohort was 25.8, which approximates the observed mean BMI in both ICE cohort arms, i.e. 26.2. Cardiovascular disease and diabetes were common in both cohorts. The Dutch part of the ICE cohort had higher mMRC scores than the Swiss part and the Swiss COPD cohort. The Swiss cohort included patients with greater airflow obstruction than that observed in the ICE cohort. There were no patients with COPD GOLD stage I in the ICE cohort (table 2); the majority had a moderate COPD stage, i.e. GOLD II (Dutch arm: 67% and Swiss arm: 63%). The Swiss cohort included COPD patients with mild to very severe airway obstruction (moderate COPD: 42.9% and severe/very severe COPD: 54.4%). GOLD stage I prevalence was 2.5% in the Swiss cohort. Mean mMRC was 1.4 in the Swiss cohort, and 1.1 and 2.3 in the Swiss and Dutch arms of the ICE cohort, respectively.

During the 2-year follow-up period, 52 (8.1%) of the patients observed according to the protocol died. The median ADO score was 7 (range 0–14, IQR 6–9). The OR for death per ADO index point increase was 1.50 [95% confidence interval (CI) 1.31–1.71]. A significant association between predicted ADO index and the observed 2-year risk of death was seen. The ROC AUC was 0.78 (95% CI 0.71–0.84; fig. 3). The predictive capacity of the 2 cohorts was similar, with an AUC of 0.76 in the Swiss COPD cohort and 0.79 in the ICE COLD ERIC.

## Discussion

The ADO index accurately predicted 2-year all-cause mortality in patients with COPD treated in the primary care setting. Our findings raise two important points. The first is the fact that the ADO index performs accurately in patients in primary care, i.e. patients cared for by their GP, and the second is that this index can be used to predict mortality over a shorter time period than that for which it was originally developed.

The ADO index is derived from three strong predictors: age, dyspnoea and airflow obstruction; Puhan et al. [5] observed that the factor most strongly associated with 3-year mortality is age, followed by $FEV_1$ and dyspnoea. These predictors are easily obtained in primary care settings, which is where the majority of COPD patients are diagnosed and managed.

The ADO index is a useful multidimensional index that includes parameters which help us to look at the patients from more than one perspective and can be obtained at a single time point. Furthermore, these parameters do not require historical data (e.g. the number of exacerbations in the past 12 months), which can be inaccurate, particularly in elderly patients with comorbid cognitive impairment. This may be particularly relevant when a new diagnosis of COPD is made or when a patient is new to the GP.

Age is a physiological parameter featuring in many chronic disease indices and scales such as the Framingham risk score, the APACHE (Acute Physiology and Chronic Health Evaluation) and the $CHADS_2$ score [17–22]. Age reflects the physiological and biological path of humans and their disease history. It is therefore a large and significant contributor to mortality risk. Comorbidities, muscle atrophy and loss as well as biological cell and system dysfunction all manifest with increasing age.

Dyspnoea is one of the most hindering symptoms of COPD. The dyspnoea grade specifies a patient's perspective of their disease and can be easily measured using the mMRC. Moreover, a previous study has shown that the mMRC dyspnoea scale provides a better prediction of mortality than $FEV_1$ [23].

Lung function, expressed by $FEV_1$, was the most commonly used prognostic factor in COPD before the development of multi-dimensional prognosis indices such as the BODE, modified BODE and ADO index. Although $FEV_1$ is widely used as a predictor for mortality and a marker for disease development, it does not reflect a patient's illness symptoms and does not correlate accurately with the subjective illness progress, affliction or quality of life [24]. Moreover, there is a poor association between the degree of dyspnoea and $FEV_1$, which indicates that a low $FEV_1$ does not mean a high grade of dyspnoea [24, 25]. We believe that multidimensional indices such as ADO or BODE could help to better manage COPD patients individually according to their own risk profile, and may help their GPs to develop new strategies for better treatment, rehabilitation and quality of life [26, 27]. Index-guided treatment algorithms, however, still require prospective evaluation in randomised controlled trials.

The ADO index has a very good 2-year mortality prediction. In COPD, there are patients who are at a higher risk of death than others within the next 2 years, and such patients can be identified by their ADO score. Poor lung function, especially a fast decline in lung function, is an important predictor for mortality in COPD [3, 28]. Our data show that a GP can even estimate a patient's 2-year mortality with the ADO index. Therefore, after having determined a patient's ADO index score, the GPs should be encouraged to reassess their current treatment. In particular, those patients who have had a greater risk of mortality predicted might indeed benefit from extended, guidelines-based treatment including pharmacological and non-pharmacological interventions [8, 12, 29].

The purpose of the ADO index is not to reflect the severity of respiratory disease. Predictive models generally try to estimate the probability of an event as accurately as possible but do not aim to establish a causal relationship or directly inform what preventive or therapeutic actions to take. ADO's purpose is to predict the probability that a COPD patient of a certain age with dyspnoea and a high level of airway obstruction will be dead before 2 (or 3) years have passed and to then use this probability to support a (shared) treatment decision, given that good evidence exists for a (fixed proportional, i.e. a relative risk reduction) treatment effect on, in this case, mortality.

Cardiovascular risk models such as the Framingham model [17] also follow the approach that we took (for ADO), commonly including non-modifiable predictors (e.g. age, sex and sometimes familial history) because these substantially improve the prediction. Sometimes prediction models include modifiable factors that add to the prediction but the modification of which may not influence the outcome to any extent that is of interest. We think that the purpose of risk prediction and what type of treatment should be given can be two separate issues, as long as there is good evidence that the probability of death within 2 years can be reduced and assuming that this reduction is worthwhile, i.e. over a threshold that takes into

account adverse effects and costs, as is the case with the Framingham and other similar cardiovascular disease models.

In COPD, treatment that improves a patient's prognosis may include smoking cessation, pulmonary rehabilitation or the administration of drugs or long-term oxygen to reduce the risk of exacerbations (and subsequently death). Thus, a prediction model such as ADO simply alerts physicians that a patient is at an increased risk of death. However, the steps then taken do not need to be restricted to modifying the predictors of the ADO index.

A strength of our study is the inclusion of 3 groups of patients from 2 countries. These 3 groups were comparable as well as being similar to other COPD cohorts described in the literature, in terms of age and comorbidities. They reflect the population of COPD patients who are treated in primary-care settings [30]. As expected, we had fewer patients with COPD stage IV than cohorts from more specialized settings [3]. A potential limitation is that the Swiss cohort and the ICE COLD ERIC had different study protocols, but, given the simplicity of the data required for the ADO index and the all-cause mortality results at 2 years, we do not think that this had an important influence on our analysis. Furthermore, the predictive capacity of the ADO index was comparable in both cohorts, evident from the fact that they had a very similar AUC.

In conclusion, the ADO index is an accurate predictor of 2-year mortality in patients with COPD treated in primary care settings. The ADO index predictors can be easily obtained in general practices, which is where the majority of COPD patients are managed.


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## Financial Disclosure and Conflicts of Interest

The funding sponsors had no obligation or any other role in the design of the study data collection, interpretation or analysis. All authors had full access to the study data and are accountable for the paper and its submission for publication.


## References


1 Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V, Buist S: Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27:397–412.
2 Mathers CD, Loncar D: Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
3 Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005–1012.
4 Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, Wedzicha JA, Price D, Hyland ME: Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. Am J Respir Crit Care Med 2009;180:1189–1195.
5 Puhan MA, Garcia-Aymerich J, Frey M, ter Riet G, Anto JM, Agusti AG, Gomez FP, Rodriguez-Roisin R, Moons KG, Kessels AG, Held U: Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet 2009;374:704–711.
6 Puhan MA, Hansel NN, Sobradillo P, Enright P, Lange P, Hickson D, Menezes AM, Riet GT, Held U, Domingo-Salvany A, Mosenifar Z, Anto JM, Moons KG, Kessels A, Garcia-Aymerich J; International CCCWG: Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts. BMJ Open 2012; 2e002152.
7 Jochmann A, Neubauer F, Miedinger D, Schafroth S, Tamm M, Leuppi JD: General practitioner's adherence to the COPD GOLD guidelines: baseline data of the Swiss COPD Cohort Study. Swiss Med Wkly 2010, Epub ahead of print.
8 Jochmann A, Scherr A, Jochmann DC, Miedinger D, Torok SS, Chhajed PN, Tamm M, Leuppi JD: Impact of adherence to the GOLD guidelines on symptom prevalence, lung function decline and exacerbation rate in the Swiss COPD cohort. Swiss Med Wkly 2012;142:w13567.
9 Siebeling L, Puhan MA, Muggensturm P, Zoller M, Ter Riet G: Characteristics of Dutch and Swiss primary care COPD patients – baseline data of the ICE COLD ERIC study. Clin Epidemiol 2011;3:273–283.
10 Siebeling L, ter Riet G, van der Wal WM, Geskus RB, Zoller M, Muggensturm P, Joleska I, Puhan MA: ICE COLD ERIC – International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts – study protocol for an international COPD cohort study. BMC Pulm Med 2009;9:15.
11 Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, Committee GS: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001;163:1256–1276.
12 Global Strategy for the Diagnosis MaPoC. Global Initiative for Chronic Obstructive Lung Disease (GOLD), updated 2013. http://www.goldcopd.org/

13 Mahler DA, Wells CK: Evaluation of clinical methods for rating dyspnea. Chest 1988;93: 580–586.
14 Eltayara L, Becklake MR, Volta CA, Milic-Emili J: Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;154: 1726–1734.
15 Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; Force ATS/ERS Task Force: General considerations for lung function testing. Eur Respir J 2005;26:153–161.
16 Braendli O, Schindler C, Kuenzli N, Keller R, Perruchoud AP: Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population. Thorax 1996;51:277–283.
17 D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB: General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–753.
18 Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS, Benjamin EJ: Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009;373:739–745.
19 Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, et al: The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100:1619–1636.
20 Teres D, Lemeshow S: The APACHE III prognostic system. Chest 1992;102:1919–1920.
21 Markgraf R, Deutschinoff G, Pientka L, Scholten T, Lorenz C: Performance of the score systems Acute Physiology and Chronic Health Evaluation II and III at an interdisciplinary intensive care unit, after customization. Crit Care 2001;5:31–36.
22 Paoletti Perini A, Bartolini S, Pieragnoli P, Ricciardi G, Perrotta L, Valleggi A, Vergaro G, Michelotti F, Boggian G, Sassone B, Mascioli G, Emdin M, Padeletti L: CHADS2 and CHA2DS2-VASc scores to predict morbidity and mortality in heart failure patients candidates to cardiac resynchronization therapy. Europace 2014;16:71–80.
23 Nishimura K, Izumi T, Tsukino M, Oga T: Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002;121:1434–1440.
24 Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK: Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297–1303.
25 Miedinger D, Linz A, Praehauser C, Chhajed PN, Buess C, Schafroth Torok S, Bucher HC, Tamm M, Leuppi JD: Patient-reported respiratory symptoms and pre-bronchodilator airflow limitation among smokers in Switzerland. Prim Care Respir J 2010;19:163–169.
26 Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, Brusasco V, Burge PS, Calverley PM, Celli BR, Jones PW, Mahler DA, Make B, Miravitlles M, Page CP, Palange P, Parr D, Pistolesi M, Rennard SI, Rutten-van Molken MP, Stockley R, Sullivan SD, Wedzicha JA, Wouters EF; American Thoracic Society, European Respiratory Society Task Force on Outcomes of COPD: Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008;31: 416–469.
27 Kent DM, Hayward RA: Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. JAMA 2007;298:1209–1212.
28 Baughman P, Marott JL, Lange P, Martin CJ, Shankar A, Petsonk EL, Hnizdo E: Combined effect of lung function level and decline increases morbidity and mortality risks. Eur J Epidemiol 2012;27:933–943.
29 Osthoff M, Jenkins C, Leuppi JD: Chronic obstructive pulmonary disease – a treatable disease. Swiss Med Wkly 2013;143:13777.
30 Sharif R, Cuevas CR, Wang Y, Arora M, Sharma G: Guideline adherence in management of stable chronic obstructive pulmonary disease. Respir Med 2013;107:1046–1052.